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EXAMINER	
FETTEROLF, BRANDON J	
ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 11/16/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/043,877	MUKHOPADHYAY ET AL.	
	Examiner	Art Unit	
	Brandon J. Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-163,166,168,171-175,183 and 184* is/are pending in the application.

4a) Of the above claim(s) *4-8,11,30-74,78-82,107-160,163,166,168 and 171-175* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,9,12-19,21-29,75-77,83-97,99-106,161,162,183 and 184* is/are rejected.

7)☒ Claim(s) *10,20 and 98* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Response to the Amendment

The Amendment filed on 08/22/2005 in response to the previous Non-Final Office Action (03/18/2005) is acknowledged and has been entered.

Claims 164-165, 167, 169-170, 176-182 have been canceled.

Claims 1-163, 166, 168, 171-175 and 183-184 are currently pending.

Claims 4-8, 11, 30-74, 78-82, 107-160, 163, 166, 168 and 171-175 are withdrawn from consideration as being drawn to a non-elected invention and/or species.

Claims 1-3, 9-10, 12-29, 75-77, 83-106, 161-162 and 183-184 are currently under consideration.

The Declaration Under CFR 1.131 filed on 08/22/2005 by the inventors is acknowledged and has been considered. The Declaration filed on 08/22/2005 under 37 CFR 1.131 is sufficient to overcome the Camden et al reference with respect to claims 1-3, 9-10 and 12-29 as specifically drawn to a method of inducing apoptosis in a cell expressing a tumor suppressor gene comprising administering an effective amount of a benzimidazole to said cell, wherein the expression of the tumor suppressor gene by the cell and the benzimidazole results in the apoptosis of the cell. However, the evidence submitted is insufficient to establish a reduction to practice of the invention in this country or a NAFTA or WTO member country prior to the effective date of the Camden reference with respect to claims 75-77, 83-106, 161-162 and 184. As noted above, the Declaration clearly shows reduction to practice of an *in vitro* method of inducing apoptosis but appears to be silent of the reduction to practice of the presently claimed *in vivo* methods recited in claims 75-77, 83-106, 161-162 and 184. While Applicants contend (Remarks, page 22) that reduction to practice is shown by the fact that the cell types used in the experiments were human cells, those of skill in the art recognize the unpredictability of extrapolating in vitro data to in vivo (see for example, Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4); Dermer (Bio/Technology, 1994, 12:320)). Moreover, Applicants contend that the law is clear that a Rule 131 Declaration need only show as much as the prior art discloses. However, contrary to

Applicants assertion, Camden discloses *in vivo* treatment (beginning on column 14, line 53 to column 25, line 6). As such, the Declaration is insufficient to overcome the Camden et al. reference with respect to these claims.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Rejections Maintained:

Claims 75-76, 83-97 and 99-100 **remain** rejected under 35 U.S.C. 102(e) as being anticipated by Camden (US 6,262,093, 1999).

Camden teaches (column 11, line 69 to column 12, line 51) a method of inducing apoptosis in cancer cells expressing abnormal p53 by administering an effective amount of a benzimidazole derivative. The patent further teaches (column 12, line 52 to column 13, line 24) a method of treating a patient having cancer expressing abnormal p53 by administering an effective amount of a benzimidazole derivative to induce apoptosis. Moreover, Camden discloses (column 14, line 53 to column 24, line 31) a method of treating a patient with cancer comprising administering an effective amount of a benzimidazole derivative. With regards to the cancer, the patent teaches that cancer includes, but is not limited to, cancers of the breast, lung, non-small cell lung and sarcoma (column 3, lines 45-50) or cancer that has survived treatment with another anticancer agent (column 29, lines 9-13). Specifically, Camden discloses the apoptotic effect in cancer cells such as, for example, MCF7 breast cells both in vitro (column 12, lines 46-51) and in vivo (column 16, lines 48+). With regards to the cancer cells, the patent teaches (column 12, lines 46-51) that some of the cancer cell lines tested are known to express abnormal p53. With regards to administration, Camden provides that 1 to 1000 mg/kg of a benzimidazole derivative (column 5, line 58 to column 6, line 17) can be administered orally, by intravenous injection, by parental administration or by injection into or around the tumor (column 6, lines 26-43). In addition, Camden teaches that the compound can be administered as a single daily dose or repeated at least once (column 6, lines 18-25). Furthermore, the patent shows that even at a concentration less than 10 μg/mL, the benzimidazole derivatives were capable of inducing apoptosis in p53 abnormal cell lines (column 12, lines 46-51). Thus, while

Camden does not characterize the breast cells as expressing the tumor suppressor gene MDA-7, the claimed functional limitation would be an inherent property of the referenced since the specification (page 14, lines 11-18) teaches that MDA-7 is expressed in human breast cancer cells. Thus, it does not appear that the claim language or limitation results in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001).

In reference to the rejection, Applicants contend (Remarks, beginning on page 16) that Camden fails to disclose each limitation of the claimed invention because it fails to expressly or inherently disclose the limitation "wherein the expression of a tumor suppressor gene by the cell and the benzimidazole results in inhibition of said cancer." For examples, Applicants argue that the sections of Camden cited by the Examiner do not appear to include any information whatsoever regarding the expression of a tumor suppressor gene, or any information correlating expression of a tumor suppressor gene with inhibition of cancer. Specifically, Applicants assert that the section cited by the Examiner (column 11, line 69 to column 12, line 51) is directed to cells expressing abnormal p53 (see, e.g., column 12, lines 49-51). Moreover, Applicants submit that Camden does not provide any information regarding measuring p53 protein or mRNA, or any results correlating p53 expression with inhibition of cancer. Furthermore, Applicants contend that Camden presents no information comparing p53 expressing cells with cells that do not express any p53. With regards to inherency, Applicants argue that for inherent anticipation to arise "the prior art necessarily function in accordance with or includes, the claimed limitation." Atlas Powder Co., 190 F.3d at 1347. (citing In re King, 801 F.2d 1324, 11326 (Fed. Cir., 1986). For example, Applicants assert that in order for Camden to fulfill inherent anticipation there must be, at the very least, expression of a tumor suppressor gene upon apoptotic cell death. Applicants submit that Camden does not appear to teach any such requirement, but instead teaches that a normal p53 gene is not required for apoptosis to occur. Moreover, Applicants submit that Camden does not anticipate the invention because it does not disclose the limitation "wherein the tumor cell is a multidrug resistant tumor cell." For example, Applicants argue that while Camden discloses the treatment of cancer with one of the specifically defined benzimidazole derivatives wherein the patient has survived treatment with another anticancer agent, Applicants contend that this is distinguishable from a tumor cell exhibiting the properties of multidrug resistance. Furthermore, Applicants submit that Camden fails to

disclose any cancer cells expressing the tumor suppressor gene MDA-7. For example, Applicants contend that while the Examiner states that all breast cancer cells express MDA-7, Applicants assert that the Examiner misinterpreted the information provided in the specification of the present invention (page 14, lines 11-18) because the statement is made in reference to Su et al. entitled, "The cancer growth suppressor gene mda-7 selectively induces apoptosis in human breast cancer cells and inhibits tumor growth in nude mice," which indicates that when breast cancer cells are infected with adenoviral vectors expressing the MDA-7 gene, the expression of this gene induces apoptosis.

These arguments have been carefully considered, but are not found persuasive.

The previous rejection was based on the technical reasoning that necessarily flowed from the prior art; e.g., a method of treating a patient having cancer expressing abnormal p53 by administering an effective amount of a benzimidazole derivative to inhibit cancer. Thus, while Applicants contend that Camden fails to disclose each limitation of the claimed invention because it fails to expressly or inherently disclose the limitation "wherein the expression of a tumor suppressor gene by the cell and the benzimidazole results in inhibition of cancer", Applicants have not clearly provided evidence or patentable difference between the instantly claimed method and that of the prior art. For example, as stated by Applicants Camden is "directed to cells expressing abnormal p53 (see, e.g., column 12, lines 49-51)". Thus, it appears that the Camden teaches cells that express abnormal p53. Moreover, in response to Applicants contention that Camden does not teach expression of a tumor suppressor gene by the cell and the benzimidazole results in inhibition of cancer, the Examiner recognizes that even though the claims are drawn to a mechanism by which cancer cells are inhibited, the claimed method does not appear to distinguish over the prior art teaching of the same or nearly the same method. For example, the specification discloses (page 65, Example 3) experiments performed *in vivo* to evaluate the anti-tumor activity of mebendazole in mice inoculated with A549 tumor cells, while Camden teaches a method of reducing tumor growth in mice models using tumor cell lines such as MXI (breast), A549 (lung) and HT29 (colon (column 23, lines 43-60). With regards to the HT29 cell line, the patent teaches that HT29 cells comprise abnormal p53 (column 11, line 65 to column 12, line 19). With regards to A549 cell line, the specification teaches (page 64, Table 4) that A549 cell line expresses wild type p53. As such, the mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render

nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145. Moreover, the office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989). In addition, in contrast to Applicants contention that Camden does not teach any information regarding measuring p53 protein or mRNA, any results correlating p53 expression with inhibition of cancer or comparing p53 expressing cells with cells that do not express any p53, the instant claims do not appear to differentiate between abnormal or wild-type tumor suppressor expression, nor do the claims which have been rejected require any type of measurement. Furthermore, Applicants argument that Camden does not anticipate the invention because multidrug resistant tumor cells exhibit properties which differ from those that have been exposed to another anticancer agent is not pertinent because Applicants have not provided any factual evidence to support these allegations. What is to say that a tumor cell which have been treated previously with chemotherapeutics have not developed resistance? The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989). Lastly, in response to Applicants assertion that the Examiner misinterpreted the information provided in the specification of the present invention regarding MDA-7 (page 14, lines 11-18), the Examiner recognizes this misinterpretation and agrees with Applicants interpretation of Su *et al.* However, while Su *et al.* indicates breast cancer cells which are infected with adenovirus vectors expressing MDA-7 gene, the reference clearly sets forth that MDA-7 is expressed in metastic

melanoma (see page 14400, 2nd column, 2nd full paragraph). Thus, in view of this and the Camden method of administering a benzimidazole derivative for the treatment of melanoma (column 23, lines 43-60), it appears that the expression of MDA-7 is an inherent property of melanoma cells. Therefore, claims 75-76, 83-100 remain rejected under 35 U.S.C. 102(e) as being anticipated by Camden (US 6,262,093, 1999)

Claims 75-76, 83-97 and 99-106 **remain** rejected under 35 U.S.C. 103(a) as being unpatentable over Camden (US 6,262,093, 1999) in combination with Perdoma *et al.* (J. Cancer Res. Clin. Oncol. 1998, 124, 10-18).

Camden teaches as set forth above with regard to claims 75-76, 83-97 and 99-100, a method of treating cancer by inducing apoptosis to a cell expressing abnormal p53 comprising administering a benzimidazole derivative.

Camden does not teach determining the tumor suppressor status by way of Southern blotting, Northern blotting, PCR, ELISA or Western blotting (claims 23-28 and 101-106).

Perdoma *et al.* teach determining the p53 status, by Western blot analysis (page 12, 3rd paragraph) or other methods such as polymerase chain reaction (PCR), could make it possible to predict the response to therapy in certain patients (page 17, 1st column, 2nd paragraph). Perdoma *et al.* further teach that the response to cisplatin *in vivo* of NSCLC tumor lines was dependent on p53 status (page 17, 1st column, 2nd paragraph). Specifically, the reference teaches wt-p53 tumors showed a regression in size of around 60%, whereas mt-p53 tumors stopped growing (page 17, 1st column, 2nd paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to determine the status of a tumor suppressor gene, like p53, in a tumor cell prior to administering a benzimidazole derivative using techniques such as Western blot, PCR or other methods of analysis. One would have been motivated to do so because Camden teaches the selectivity in killing p53 abnormal cell lines versus cells expressing normal p53 (column 12, lines 52+), while Perdoma *et al.* teaches that the "response to cisplatin *in vivo* of tumors derived from different NSCLC lines was dependent on p53 status (page 17, 1st column, 2nd paragraph)." Further, one of ordinary skill in the art would have a reasonable expectation of success because Perdoma *et al.* teaches "analysis of p53 status, by immunohistochemical or other methods such as the

polymerase chain reaction *(PCR)*, could make it possible to predict the response to therapy in certain patients (page 17, 1st column, 2nd paragraph)."

In reference to the rejection, Applicants contend that a prima facie case of obviousness has not been established because the prior act reference cited by the Examiner do not teach or suggest all of the claim limitation. For the reasons set forth above, Applicants contend that the Examiner has not shown that Camden teaches or suggest inhibition of cancer as the result of expression of a tumor suppressor gene and the administration of a benzimidazole. Nor does Camden teach the particular benzimidazoles found in claims 161-162 and 183 or the limitation "wherein the tumor cell is a multidrug resistant tumor cell. Moreover, Applicants argue that Perdomo does not teach or suggest the missing limitations that are not disclosed in Camden. For example, Applicants assert that the Examiner has not shown where Perdomo includes any information pertaining to benzimidazoles, or the effect of benzimidazoles on tumor cells, nor do Applicants find any such disclosure in Perdomo. Lastly, Applicants argue that Perdomo provides no motivation to one of ordinary skill in the art to provide the limitation since it does not even address benzimidazoles.

These arguments have been carefully considered, but are not found persuasive.

First, Applicants arguments pertaining to Camden have been addressed by the Examiner above and have been incorporated herein. Secondly, while the Examiner concedes that Perdoma does not teach any information pertaining to benzimidazoles, or the effect of benzimidazoles on tumor cells, Applicants appear to be considering the references individually. However, the courts have held that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. In re Keller, 642 F.2d 13, 208 USPQ 871 (CCPA 1981); In re Merck & Co., Inc., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In response to Applicants argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the motivation lies within Perdoma whom teaches that the analysis of p53 status could make it possible to predict the response to therapy in certain patients. As such, claims 75-76, 83-106, 161-162 remain and new claim 183 is rejected under

35 U.S.C. 103(a) as being unpatentable over Camden (US 6,262,093, 1999) in combination with Perdoma *et al.* (J. Cancer Res. Clin. Oncol. 1998, 124, 10-18).

Claims 75-77, 83-97, 99 and 161-162 **remain** and **new** claim 184 is rejected under 35 U.S.C. 103(a) as being unpatentable over Camden (US 6,262,093, 1999) in combination with Delatour *et al.* (IDS, Therapie 1976; 31 (4); 505-515).

Camden teaches as set forth above with regard to claims 75-76, 83-97 and 99-100, a method of treating cancer by inducing apoptosis to a cell expressing abnormal p53 comprising administering a benzimidazole derivative. Camden does not teach that the benzimidazole derivative is , mebendazole.

Delatour *et al.* teach the ebryotoxic and antimitotic properties of benzimidazole compounds (title). Specifically, the reference discloses that in mice with Ehrich carcinoma mebendazole inhibited tumor growth and increased survival time (abstract).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to include mebendazole as taught by Delatour *et al.* in the method taught by Camden. One would have been motivated to make these modifications because as evidenced by Delatour *et al.*, benzimidazole derivatives such as mebendazole have been shown to inhibit tumor growth. Thus, one of ordinary skill in the art would have a reasonable expectation of success that using mebenzdazole as taught by Delatour *et al* in the method taught by Camden, one would achieve an additional benzimidazole derivative that induces apoptosis in cells and tumors expressing abnormal p53.

In reference to the rejection, Applicants contend that a prima facie case of obviousness has not been established because the prior act reference cited by the Examiner do not teach or suggest all of the claim limitation. For the reasons set forth above, Applicants contend that the Examiner has not shown that Camden teaches or suggest inhibition of cancer as the result of expression of a tumor suppressor gene and the administration of a benzimidazole. Nor does Camden teach the particular benzimidazoles found in claims 161-162 and 183 or the limitation "wherein the tumor cell is a multidrug resistant tumor cell. Moreover, Applicants argue that Delatour includes no information pertaining to induction of apoptosis as a result of administration of a benzimidazole and expression of a tumor suppressor gene. Applicants further assert that Delatour does not include any

information pertaining to inhibition of cancer as a result of expression of a tumor suppressor and administration of a benzimidazole.

These arguments have been carefully considered, but are not found persuasive.

First, Applicants arguments pertaining to Camden have been addressed by the Examiner above and have been incorporated herein. In response to Applicants Arguments that Delatour does not include any information pertaining to induction of apoptosis, the examiner recognizes the *prima facie* case of obviousness was made because the benzimidazole derivatives disclosed by both Camden and Delatour *et al.* have close structural similarities and similar utilities. Moreover, the courts have held that "An obviousness rejection based on similarity in chemical structure and function entails the motivation of one skilled in the art to make a claimed compound, in the expectation that compounds similar in structure will have similar properties." In re Payne, 606 F.2d 303, 313, 203 USPQ 245, 254 (CCPA 1979). See In re Papesch, 315 F.2d 381, 137 USPQ 43 (CCPA 1963) (discussed in more detail below) and In re Dillon, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1991) (discussed below and in MPEP § 2144) for an extensive review of the case law pertaining to obviousness based on close structural similarity of chemical compounds. See also MPEP § 2144.08, paragraph II.A.4.(c). As such, Claims 75-77, 83-99 and 161-162 are rejected under 35 U.S.C. 103(a) as being unpatentable over Camden (US 6,262,093, 1999) in combination with Delatour *et al.* (IDS, Therapie 1976; 31 (4); 505-515).

New Rejections necessitated by amendment and upon discovery of new prior art:

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 9 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "the dose of benzimidazole is at least 0.05 mg/mL" in claim 9 renders the claim indefinite. The phrase "the dose of benzimidazole is at least 0.05 mg/mL" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. In the instant case, the claim appears to be describing a dose of the benzimidazole in terms of a concentration. However, it is unclear what the actual dose will be. Identifying an amount, i.e. volume, of the dose, which will be given, may alleviate the rejection.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 161-162, 183 and 184 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **THIS IS A NEW MATTER REJECTOIN.**

Amended claim 161 and claims 183-184 are drawn to a benzimidazole derivative having a particular formula with a provisio limitation setting forth that if R^3 is a H or chloro, then R^2 cannot be H if R^1 is carbamate. Applicants contend that written description support for the structural limitations can be found generally throughout the specification, such as on page 8, line 5 through page 9, line 22. Applicants further submit that they are not required to explicitly recite the exact language of the proviso in the specification. Moreover, Applicants assert that one of ordinary skill in the art, upon reading the specification, particularly the section cited herein, would have clearly recognized that Applicants contemplated the inclusion of benzimidazoles of the structure set forth in amended claims 161 (and depended claim 162 and new claims 183-184) for inclusion of the method set forth therein.

These arguments have been considered, but are not found persuasive for the reasons set forth below.

A careful review of the specification teaches the following: (1) the discovery that the

benzimidazoles (BZs), fenbendazole (FZ) and mebendazole (MZ) can increase the expression of tumor suppressor genes and greatly augment the sensitivity of tumor cells to apoptosis induction (page 8, lines 21-22 and page 9, lines 24-26; figures 1A-B, 2); (2) the structural formula of the benzimidazoles of interest having variable R^3 groups, R^1 groups and R^2 groups (page 10, lines 16+). Thus, while it is clear that the specification teaches a generic chemical formula, there does not appear to be any recitation of the negative limitation on page 8, line 5 through page 9, line 22 or generally throughout. Furthermore, the Examiner agrees with Applicants assertion that they are not required to explicitly recite the negative, i.e. proviso, limitation. However, the specification does not appear to reasonably convey to one of skill in the art that the Applicants contemplated the inclusion of the benzimidazole derivatives having the negative limitation as recited in amended claim 161. For example, it appears from the specification that the preferred benzimidazole derivatives are mebendazole and fenbendazole. However, these two compounds do not meet the negative limitations set forth in amended claim 161. Applicant is invited to point to clear support or specific examples of the claimed limitation in the specification as-filed or remove such amendatory language in response to this action.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2, 12, 15-19, 21, 29, 75-76, 83, 85, and 88-96 are rejected under 35 U.S.C. 102(b) as being anticipated by Camden (US 5,880,144, 1999).

Camden teaches a method of killing lung tumor cells (A-549), breast tumor cells (MCF-7) and colon tumor cells comprising administering a benzimidazole derivative (column 6, lines 64 to 67, and column 7, Table 3). The patent further teaches a method of treating a patient having cancer comprising administering an effective amount of a benzimidazole derivative to inhibit the growth of the cancer (abstract). With regards to administration, Camden teaches (column 5, lines 1-10) that

the benzimidazole derivatives can be administered orally, by intravenous injection, by parental administration or by injection into or around the tumor. Although Camden does not specifically teach that the administration of benzimidazole induces apoptosis, the claimed functional limitation would be an inherent property of the referenced method because as evidenced by Camden (US Patent 6,262,093, 1999), the administration of benzimidazole derivatives results in apoptosis (see column 11, line 65 to column 12, line 51). Thus, it does not appear that the claim language or limitation results in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001). Moreover, while Camden does not explicitly characterize the tumor cell lines as expressing a tumor suppressor gene such as p53, the claimed functional limitation would be an inherent property of the referenced method since the specification discusses (page 64, Table 4) that A459 tumor cells express wild-type p53. Thus, it does not appear that the claim language or limitation results in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001).

Hence, even though the claims are drawn to a mechanism by caner cells are inhibited, the claimed method does not appear to distinguish over the prior art teaching of the same or nearly the same method. The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the

subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 3, 77, 161-162 and 182-183 are rejected under 35 U.S.C. 103(a) as being unpatentable over Camden (US 5,880,144, 1999) in combination with Delatour *et al.* (IDS, Therapie 1976; 31 (4); 505-515) of record or Nasr *et al.* (Journal of Pharmaceutical Sciences 1985; 74: 831-836).

Camden teaches, as set forth above for claims 1-2, 12, 15-19, 21, 29, 75-76, 83, 85, and 88-96, a method of killing lung tumor cells (A-549), breast tumor cells (MCF-7) and colon tumor cells comprising administering a benzimidazole derivative (column 6, lines 64 to 67, and column 7, Table 3). The patent further teaches a method of treating a patient having cancer comprising administering an effective amount of a benzimidazole derivative to inhibit the growth of the cancer (abstract). With regards to administration, Camden teaches (column 5, lines 1-10) that the benzimidazole derivatives can be administered orally, by intravenous injection, by parental administration or by injection into or around the tumor.

Camden does not disclose other benzimidazole derivatives such as mebendazole.

Delatour *et al.* teach the ebryotoxic and antimitotic properties of benzimidazole compounds (title). Specifically, the reference discloses that a method of inhibiting tumor growth in mice comprising administering the benzimidazole derivative, mebendazole (abstract).

Nasr *et al.* teach (page 831, paragraph bridging 1st column and 2nd) *in vivo* anticancer activity correlation of aromatic, aliphatic, and heterocyclic carbamates and their thio-isosters against both intraperitoneally implanted murine P-388 lymphocytic leukemia and L-1210 lymphoid leukemia. Specifically, the reference teaches anticancer activity of benzimidazole carbonates (page 834, Table VIII and page 835, 2nd column, 2nd full paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the references so as to inhibit tumor growth because each of the benzimidazole derivatives disclosed by the references have close structural similarities and similar utilities. In the instant case, the courts have held that "An obviousness rejection based on similarity in chemical structure and function entails the motivation of one skilled in the art to make a claimed compound, in the expectation that compounds similar in structure will have similar properties." In re Payne, 606 F.2d 303, 313, 203 USPQ 245, 254 (CCPA 1979). See In re Papesch, 315 F.2d 381, 137 USPQ 43 (CCPA 1963); In re Dillon, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1991) (see in

MPEP § 2144) for an extensive review of the case law pertaining to obviousness based on close structural similarity of chemical compounds. See also MPEP § 2144.08, paragraph II.A.4.(c). Thus, one of skill in the art would have a reasonable expectation of success that by substituting a benzimidazole derivate as taught by Delatour et al. or Nasr et al. in the method of Camden, one would achieve a method of inhibiting the growth of cancer.

Claims 23-28 and 101-106 are rejected under 35 U.S.C. 103(a) as being unpatentable over Camden (US 5,880,144, 1999) in combination with Delatour *et al.* (IDS, Therapie 1976; 31 (4); 505-515) of record or Nasr et al. (Journal of Pharmaceutical Sciences 1985; 74: 831-836) in view of Perdoma *et al.* (J. Cancer Res. Clin. Oncol. 1998, 124, 10-18) of record.

The combination of Camden and Delatour et al. or Nasr et al. teach, as set forth above with regard to claims 1-3, 12, 15-19, 21, 29, 75-77, 83, 85, 88-96, 161-162 and 182-183, a method of killing lung tumor cells, breast tumor cells and colon tumor cells comprising administering a benzimidazole derivative. The patent further teaches a method of treating a patient having cancer comprising administering an effective amount of a benzimidazole derivative to inhibit the growth of the cancer (abstract).

The combination of Camden and Delatour et al. or Nasr et al. does not teach determining the tumor suppressor status by way of Southern blotting, Northern blotting, PCR, ELISA or Western blotting (claims 23-28 and 101-106).

Perdoma *et al.* teach determining the p53 status, by Western blot analysis (page 12, 3rd paragraph) or other methods such as polymerase chain reaction (PCR), could make it possible to predict the response to therapy in certain patients (page 17, 1st column, 2nd paragraph). Perdoma *et al.* further teach that the response to cisplatin *in vivo* of NSCLC tumor lines was dependent on p53 status (page 17, 1st column, 2nd paragraph). Specifically, the reference teaches wt-p53 tumors showed a regression in size of around 60%, whereas mt-p53 tumors stopped growing (page 17, 1st column, 2nd paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to determine the status of a tumor suppressor gene, like p53, in a tumor cell prior to administering a benzimidazole derivative using techniques such as Western blot, PCR or other methods of analysis. One would have been motivated to do so because as taught by Perdoma

et al., analysis of p53 status, by immunohistochemical or other methods such as the polymerase chain reaction *(PCR)*, could make it possible to predict the response to therapy in certain patients (page 17, 1st column, 2nd paragraph). Thus, one of skill in the art would have a reasonable expectation of success that by measuring the status of the tumor suppressor gene in view of Perdoma, one would achieve an effective method of predicting the outcome of benzimidazole therapy.

Claims 13-14 and 86-87 are rejected under 35 U.S.C. 103(a) as being unpatentable over Camden (US 5,880,144, 1999)in combination with Delatour *et al.* (IDS, Therapie 1976; 31 (4); 505-515) of record or Nasr et al. (Journal of Pharmaceutical Sciences 1985; 74: 831-836) in view of Lucci et al. (Cancer; 86:300-311, published online on November 2000).

The combination of Camden and Delatour et al. or Nasr et al. teach, as set forth above with regard to claims 1-3, 12, 15-19, 21, 29, 75-77, 83, 85, 88-96, 161-162 and 182-183, a method of killing lung tumor cells, breast tumor cells and colon tumor cells comprising administering a benzimidazole derivative. The patent further teaches a method of treating a patient having cancer comprising administering an effective amount of a benzimidazole derivative to inhibit the growth of the cancer (abstract).

The combination of Camden and Delatour et al. or Nasr et al. does not teach that the tumor cell is a multidrug resistant tumor cell, wherein the tumor cell is a breast tumor cell.

Lucci et al. teach multidrug resistance modulators and doxorubicin synergize to elevate ceramide levels and elicit apoptosis in drug-resistant cancer cells, specifically drug resistant human breast cancer cells lines. Moreover, the reference teaches that multidrug resistance is a formidable roadblock to the effective treatment of cancer by conventional chemotherapy, wherein the resistance complicates treatment in many instances (page 300, 1st paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use a multidrug resistant cell line, such as a breast cancer cell, in the method taught by Camden in view of the teachings of Lucci et al. One would have been motivated to do so because as taught by Lucci, multidrug resistance is a formidable roadblock to the effective treatment of cancer by conventional chemotherapy, wherein the resistance complicates treatment in many instances. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by administering a benzimidazole derivative to multidrug resistant cell, one would achieve a method

of inhibiting tumor growth in a patient that has already become resistant to conventional chemotherapy.

Note: Claims 10, 20 and 98 are objected to as being dependent from a rejected independent claim.

All other rejections and/or objections are withdrawn in view of applicant's amendments and arguments there to.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 8:30 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeff Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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11/14/05